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EXAMINER	
YU, MELANIE J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,528	SU ET AL.	
	Examiner	Art Unit	
	Melanie Yu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-33 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-33 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 13 June 2005 has been entered. Claims 1 and 34-37 are canceled. Claims 2, 4-10, 12-17, 21-27, 29 and 31 are currently amended. Claim 38 is new. Claims 2-33 and 38 are currently pending.

Withdrawn Rejections

1. Previous rejections of claims 1-38 under 35 USC 112, second paragraph, 35 USC 102(e) and 35 USC 103(a) have been withdrawn in light of applicant's amendment.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 2-33 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 14 and 15, the phrases "a plurality of the discrete locations" and "a plurality of discrete protein enriched locations" are vague because it is unclear whether the claims are referring to the plurality of discrete protein enriched locations of claim 38 or whether a separate plurality of discrete protein locations exist.

Claim 38 is vague because it is unclear whether the "a discrete protein enriched location" recited in line 2 of part e) of the claim is the same discrete protein enriched location created in by depositing each fraction at a discrete location in part b. The claim recites "the chemical composition" in line 3 of part e, and "the corresponding" in line 4 of part e of the claim. There is insufficient antecedent basis for this limitation in the claim.

With respect to claim 25, it is unclear whether the method of claim 38 further comprises maintaining the separated proteins in a separated state or whether the step of depositing includes the step of maintaining.

Claim Rejections - 35 USC § 103

3. Claim 2-5, 10, 14-17, 20-26, 29-33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Carron (US 5,693,152).

Natan et al. teach a method for analyzing the protein content of a biological sample (col. 10, lines 40-47 describe the sandwich assay; col. 10, line 52 describes the target analyte being a protein), comprising: separating proteins in a sample (separates target analyte based on chemical interaction, col. 23, lines 45-48; ligands for different target analyte must be separated in order for attachment at specific locations, col. 3, lines 23-26; ligands can be proteins, col. 10, lines 40-47); depositing proteins in a separated state at discrete locations on a solid substrate (ligands are attached at specific locations, therefore ligands can be samples in each well which are maintained without cross contamination, col. 25, lines 1-4); contacting the separated proteins deposited at the plurality of discrete protein enriched locations with probes under conditions suitable to form a capture probe/protein complex at one or more of the discrete locations (col. 3, lines 47-54; col. 10, lines 58-64; at col. 13, lines 45-52 any one of the participants can be immobilized to the substrate surface, a ligand is then bound to the immobilized receptor, protein); contacting the complexes with a Raman-active probe construct that binds to the complex (col. 3, lines 54-63; col. 13, lines 45-52, an Au-conjugated antibody is conjugated with the ligand, which is bound to the immobilized receptor, protein); and detecting Raman spectra produced by the probe construct/protein complexes at the plurality of discrete locations, wherein

a Raman spectrum from at a discrete location provides information about the chemical composition of a protein the corresponding discrete protein enriched location by analyzing the protein content of a complex biological sample (col. 23, lines 58-61 discloses SERS detection; Fig. 12 discloses an amplified detection after an unamplified detection; furthermore a change in resonance is detected as the target is brought in contact with the Raman-active probe, therefore the SERS detection occurs before and after contacting the proteins with capture probes and Raman active probes, col. 18, lines 1-5; surface chemical interactions are analyzed, col. 35, lines 1-5; compounds are identified, col. 24, lines 1-5). Natan et al. fail to teach chromatographically separating proteins and protein fragments in the sample into a plurality of fractions.

Carron teaches chromatographically separating compounds in a sample into a plurality of fractions, each fraction containing an individual compound (col. 3, line 54-col. 4, line 1), in order to perform chemical analysis of raw samples and separate the component to be analyzed.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the separation of proteins of Natan et al., chromatographic separating compounds into a plurality of fractions, each fraction containing an individual compound as taught by Carron, in order to allow the different ligands (proteins) to more accurately separated analyze chemical interactions of different proteins.

With respect to claims 3-5, Natan et al. teaches the capture probe being a primary antibody that binds specifically to the protein in the complex (immobilized receptor is a protein, primary antibody is ligand, col. 13, lines 45-52), and the Raman-active probe construct comprising a secondary antibody as probe and a Raman tag (secondary antibody is antibody conjugated to Au, col. 13, lines 50-52). Natan et al. also teaches the Raman-active probe being a

composite organic-inorganic nanoparticle (organic portion is the secondary antibody conjugated to the inorganic portion of gold or silver particle; col. 15, lines 28-29).

With respect to claim 10, 14-17, Natan et al. teach a substrate coated with one or more organic or inorganic materials prior to immobilization of proteins (gold evaporated onto glass substrate, col. 24, lines 40-44). Natan et al. further teaches the substrate comprised of a plurality of discrete locations on a flat plate (wells, col. 24, line 66-col. 25, line 5), and detection automated to accomplish high throughput scanning at a plurality of discrete protein enriched locations (col. 23, lines 63-66; col. 26, lines 39-48). Natan et al. also teaches the substrate comprising gold (gold evaporated on glass; col. 24, lines 41-44) and contacting the proteins at the discrete locations with silver nanoparticles (col. 16, lines 45-53).

Regarding claims 20-26, Natan et al. teach the Raman spectra being a SERS spectra (col. 23, lines 58-61), and collecting the SERS spectra from the discrete locations to compile a protein profile of the sample (col. 25, lines 1-5) and the Raman spectra and locations of the proteins on the solid substrate are recorded and correlated (col. 23, line 62-col. 24, line 7). Natan et al. further teach collection being automated to accomplish high throughput SERS spectra screening of the discrete locations (SERS can be used as well as SPR using the PDMS microwell arrays for high throughput screening, col. 23, lines 58-61). Natan et al. also teach the spectrum containing information regarding a protein characteristic of identification of the protein (sensors are used to detect unique compounds, which can be proteins, col. 24, lines 1-5). Maintaining the separated proteins in a separated state comprises depositing each fraction at a discrete location within at least one stream of flowing liquid in a microfluidic system to create a plurality of discrete protein enriched locations (proteins are separated and introduced to a flow cell in order to immobilize to

a substrate, col. 29, lines 29-52). Further comprising mixing the stream of flowing liquids comprising the separated proteins with a stream of flowing metal colloids by combining streams under conditions suitable for contacting the separated proteins with the metal colloids and the detection is SERS detection (nanoparticles introduced into flow cell where the stream of separated proteins are already located, col. 29, lines 4-52).

With respect to claims 2 and 29-33, Natan et al. teach a sample being a patent sample of blood (col. 15, lines 15-23). Natan et al. also teach creating a protein profile of the sample based on data obtained from the Raman spectra (col. 23, lines 58-61; col. 24, lines 1-6), and repeating the method using a variety of different patient samples to create a protein library containing a plurality of different protein profiles (sensor combine to form a library of ingredients, proteins, in the sample, col. 24, lines 4-6). Natan et al. further teach the comparing the protein profile of the sample with one or more protein profiles of the library to detect a difference indicative of a disease (asthma, col. 15, lines 23-31).

4. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Carron (US 5,693,152), as applied to claim 38, further in view of Grow (US 6,040,191).

Natan et al. in view of Carron, as applied to claim 38, teach a method for analyzing protein content of a biological sample, but fail to teach denaturing proteins in the sample.

Grow teaches contacting proteins in a sample prior with a denaturing agent denaturing proteins in a sample (chemicals are denaturing agent, col. 18, lines 54-58; col. 11, lines 14-20 and 26-42), in order to determine different unique structures of biological conformation of a biological-analyte complex.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al. in view of Carron, denaturing proteins before separation as taught by Grow, in order to prevent false responses due to proteins being denatured, inactivated, poisoned or leached.

Regarding claim 6, Grow teaches a biological-analyte, protein, solubilized in an aqueous solution (col. 20, lines 32-39).

With respect to claims 8 and 9, Grow teaches a denaturing agent being surfactants (col. 56, lines 28-31), and denatured proteins dried on a substrate prior to detection of signals (col. 25, line 56-col. 26, line 5).

5. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Carron (US 5,693,152), as applied to claim 38, further in view of Avseenko et al. (Immobilization of Proteins in Immunochemical Microarrays Fabricated by Electrospray Deposition, Analytical Chemistry, 2001, 73, 6047-6052).

Natan et al. in view of Carron, as applied to claim 38, teach a method for analyzing protein content of a biological sample without denaturing, but fail to teach separated proteins deposited using wet electrospray.

Avseenko et al. teach separated proteins deposited without denaturing using wet electrospray deposition (pg. 6048, right column, *Fabrication of Microarrays*, electrospray deposition of protein) onto an aluminum substrate (pg. 6048, left column, *Materials*, aluminized mylar film), in order to fabricate protein microarrays for immunochemical analysis.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al. in view of Carron, deposition of

proteins without denaturing using wet electrospray deposition as taught by Avseenko et al., in order to reduce spot size, increase fabrication rate, and simultaneously manufacture thousands of identical microchips while retaining ability to specifically bind antibodies.

Avseenko et al. also teach less preferable alternatives to deposition of proteins including contact writing (microcontact printing, pg. 6047, last paragraph left column-first paragraph, right column).

6. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Carron (US 5,693,152), as applied to claim 38, further in view of Storhoff et al. (US 2004/0053222).

Natan et al. in view of Carron, as applied to claim 38, teach a method for analyzing protein content of a biological sample, but fail to teach contacting nanoparticles with at least one chemical enhancer salt.

Storhoff et al. teach gold nanoparticles contacted with at least one chemical enhancer salt of LiCl (paragraph 0049), in order to allow a sufficient number of additional polyanionic polymer conjugates, wherein the polymer conjugates are proteins (paragraph 0053), to bind to the nanoparticles.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al. in view of Carron, nanoparticles contacted with a solution containing at least one chemical enhancer salt as taught by Storhoff et al., in order to increase stability of nanoparticles while binding proteins.

7. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natan et al. (US 6,579,721) in view of Carron (US 5,693,152), as applied to claim 38, further in view of Nelson et al. (US 5,955,729).

Natan et al. in view of Carron, as applied to claim 38, teach a method for analyzing protein content of a biological sample, but fail to teach analyzing separated proteins by mass spectroscopy.

Nelson et al. teach performing surface plasmon resonance-mass spectroscopy by detecting particles using SPR to detect the changes in the refractive index of the solution close to the surface of the sensor chip, and analyzing separated proteins by mass spectroscopy, to identify the presence of non-targeted ligands and to correct them for quantitative techniques.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the method of Natan et al. in view of Carron, analyzing separated proteins by mass spectroscopy as taught by Nelson et al., in order to quantify the amount of analyte in the sample and to provide real-time information regarding molecular interactions.

Nelson et al. teach compiling data from the mass spectroscopy with data from SPR (Fig. 4, relative intensity and resonance signals are compared, col. 4, lines 58-64), and according to Natan et al. an SERS measurement can be used instead of an SPR measurement in order to accommodate other surface-sensitive analytical techniques (col. 23, lines 54-61).

Response to Arguments

8. Applicant's arguments and amendments, see pages 11-15, filed 13 June 2005, with respect to the rejection(s)of claim(s) 1-33 under 35 USC 102(e) and 35 USC 103(a) have been

fully considered and the rejections have been withdrawn. Applicant argues that Natan fails to teach a method that includes chromatographically separating proteins and protein fragments as recited in the newly added claim 38. Such an argument is not persuasive for the stated in the rejection above. However, a new rejection has been made in view of Applicant's amendment requiring chromatographic separation.

Conclusion

No claims are allowed.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melanie Yu whose telephone number is (571) 272-2933. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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